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Effects of Diptheria-Tetanus-Pertussis or Tetanus Vaccination on Allergies and Allergy-Related Respiratory Symptoms Among Children and Adolescents in the US

Background: Findings from animal and human studies confirm that diptheria and tetanus toxoids and pertussis (DTP) and tetanus vaccinations induce allergic responses; associations between childhood vaccinations and subsequent allergies have been reported recently.

Objective: The association of DTP or tetanus vaccination with allergies and allergy related respiratory symptoms among children and adolescents in the US was assessed.

Methods: Data were used from the Third National Health and Nutrition Examination Survey on infants aged 2 months through adolescents aged 16 years. DTP or tetanus vaccination, lifetime allergy history, and allergy symptoms in the past 12 months were based on parental or guardian recall. Logistic regression modeling was performed to estimate the effects of DTP or tetanus vaccination on each allergy.

Results: The odds of having a history of asthma was twice as great among vaccinated subjects than among unvaccinated subjects (adjusted odds ratio, 2.00; 95% confidence interval, 0.59 to 6.74). The odds of having had any allergy-related respiratory symptom in the past 12 months was 63% greater among vaccinated subjects than unvaccinated subjects (adjusted odds ratio, 1.63; 95% confidence interval, 1.05 to 2.54). The associations between vaccination and subsequent allergies and symptoms were greatest among children aged 5 through 10 years.

Conclusions: DTP or tetanus vaccination appears to increase the risk of allergies and related respiratory symptoms in children and adolescents. Although it is unlikely that these results are entirely because of any sources of bias, the small number of unvaccinated subjects and the study design limit our ability to make firm causal inferences about the true magnitude of effect.

Hurwitz EL, Morgenstern H. Journal of Manipulative and Physiological Therapeutics. February 2000; Vol. 23, No. 2, pp. 81-90.

Do DTP and Tetanus Vaccinations Cause Asthma? New Study Shows Vaccinated Children Twice as Likely to Get Asthma and Other Allergy-Related Symptoms

A new study in the Journal of Manipulative and Physiological Therapeutics (authors are Eric Hurwitz, DC, PhD and Hal Morgenstern, PhD, both of UCLA School of Public Health, Department of Epidemiology) supports the findings of three previous studies that children who receive diptheria-tetanus-pertussis (DPT) or tetanus vaccines are more likely to have a "history of asthma" or other "allergy-related respiratory symptoms."

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http://www.chiroweb.com/archives/18/07/05.html

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Thursday August 13 6:18 PM EDT

``Small'' allergy risk from pertussis vaccine

NEW YORK, Aug 13 (Reuters) -- Pertussis ("whooping cough") vaccines may cause only a slight increase in the risk of allergic conditions in children, according to a study, in contrast to a previous report that suggested a large increase might occur after immunization.

Because whooping cough is a serious disease that can cause complications in infants, ``there seems to be little reason to withhold pertussis vaccination from infants, irrespective of family history of allergy," reported Dr. Lennart Nilsson and colleagues in the Archives of Pediatrics and Adolescent Medicine.

In a study of 669 Swedish children, some were given acellular pertussis vaccines, others whole cell pertussis vaccines, and some a placebo consisting of diphtheria and tetanus without the pertussis component. Acellular pertussis vaccines contain fewer bacterial proteins, and are generally considered to have fewer side effects than whole cell vaccines.

By age 2-1/2, about 30% of the youngsters in each group showed a tendency to develop allergic conditions such as hayfever, food allergy, hives or eczema.

Analysis of the study data suggests that the whole cell vaccine increased the risk of atopy (allergic conditions) by 4% or less, and the acellular pertussis vaccines increased the risk by 10%, according to the researchers from University Hospital in Linkoping, Sweden.

``Our results indicate a possible small increase in the risk of atopic disease after acellular pertussis vaccines," the authors wrote.

``Whooping cough is a debilitating disease and, in infancy, there may be serious complications," write the researchers. "The reasonable conclusion seems to be that acellular vaccines would at most be associated with a small to moderate increase in (allergy-related disorders)."

SOURCE: Archives of Pediatrics and Adolescent Medicine 1998;152:734-738.

BMJ 1998;317:205 (18 July)

Letters

Childhood vaccination should have been included in asthma study

Kaur et al's finding that children aged 12-14 years in cities had less asthma (30.3%) than those in rural areas (35%)1 must lead to questions about the role of air pollution in asthma. What I found disappointing was the absence in the questionnaire of any questions about childhood vaccination. Odent found that children aged 8 years who had been immunised against whooping cough as babies had nearly six times the incidence of asthma compared with children who were not immunised.2 And in Christchurch, New Zealand, the Wellington asthma research group studied 1265 children aged 10 years3 and found that none of the 23 children who had not received diphtheria, pertussis, and tetanus or polio immunisations had recorded consultations for asthma or other allergic illnesses whereas 23% of the immunised children had had episodes of asthma and 30% had had consultations for other allergic illnesses.

These reports point a strong finger of suspicion at childhood immunisation being the cause of the remarkable increase in childhood asthma and allergies over the past few decades. A thorough programme of unbiased research into the short and long term side effects of childhood immunisation is essential. To continue saying that vaccinations are safe in the absence of sound clinical evidence may be no truer than the claim of the emperor that his new clothes were the finest ever made. Robert Blomfield, Retired homoeopathic general practitioner.
Hebden Bridge, West Yorkshire

Kaur B, Anderson HR, Austin J, Burr M, Harkins LS, Strachan DP, et al. Prevalence of asthma symptoms, diagnosis and treatment in 12-14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). BMJ 1998; 316: 118-124[Abstract/Full Text]. (10 January.)

Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? JAMA 1994; 272: 592-593.

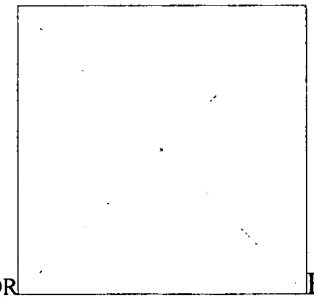
Kemp T, Pearce N, Fitzharris P, Crane J, Fergusson D, St George I, et al. Is infant immunization a risk factor for childhood asthma or allergy? Epidemiology 1997; 8: 678-680[Medline].

This article has been cited by other articles:
Mansoor, O. D. (1999). Selective evidence was used to support link between immunisation and asthma. BMJ 318: 193-193 [Full text]
Electronic responses to this article:
Read all electronic responses
Untitled
Dr Osman David Mansoor

<vardef id="TEXT">*BMJ* 1999;318:193 (16 January)

Letters

Selective evidence was used to support link between immunisation and asthma



<TXT>EDITOR Blomfield says that there is accumulating evidence that immunisation causes asthma.[1] But he presents only evidence supporting the hypothesis when there is also evidence against it.

He quotes a retrospective cohort study that suggested a link between pertussis immunisation and asthma but not the subsequent randomised controlled trial that found no association.[2] The findings of the New Zealand cohort study were based on only 23 children who did not receive triple (diphtheria, pertussis, and tetanus) vaccine or polio vaccine, for six of whom data were incomplete.[3] If even one of these children developed asthma, the association with immunisation would not be significant. The cohort study has other important limitations.[4] Furthermore, a British cohort study found no association between immunisation and wheeze but did find a lower risk of eczema among immunised children.[5]

Further research is clearly needed in this area. It is misleading to present only the evidence supporting the hypothesis when there is at least as much opposing it.

Osman David Mansoor, *Public health physician.*
Ministry of Health, PO Box 5013, Wellington, New Zealand

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Related letters in BMJ:

Childhood vaccination should have been included in asthma study

Robert Blomfield
BMJ 1998 317: 205. [Letter]

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eBMJ, 27 Jul 1998 [Response]
Related letters in BMJ:
Selective evidence was used to support link between immunisation and asthma
Osman David Mansoor
BMJ 1999 318: 193. [Letter]
Other related articles in BMJ:
GENERAL PRACTICE
Prevalence of asthma symptoms, diagnosis, and treatment in 12-14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK).
Balvinder Kaur, H Ross Anderson, Jane Austin, Michael Burr, Leigh S Harkins, David P Strachan, and John O Warner
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11. A primary peptide library, KNDXXXXXXX-COOH, where X indicates all amino acids except Cys and Trp, was first used to screen peptides that bind specifically to the glutathione-S-transferase (GST)–PDZ domains. All the peptides in the library end with free carboxylate, therefore orienting all binding pockets. The peptides that bound were sequenced as a mixture, and the selectivities for amino acids at a given position were determined by comparison to the sequence of control experiments with GST alone (*10*). Arg was not included in the calculation because of buffer contamination during sequencing. A secondary library, KNDXXXXX(S,T,Y)XX-COOH, where the −2 position was fixed with Ser, Thr, and Tyr, was used to further define the preference of some PDZ domains.
12. Peptide library synthesis was as described (*10*). Individual PDZ domains were expressed and purified as GST fusion proteins: murine hDlg PDZ-1 (186–282), PDZ-2 (281–377), PDZ-3 (428–518), and PDZ-1/2 (281–518); murine PTPbas PDZ-3 (1351–1445) and PDZ-5 (1758–1848); murine Tiam-1 PDZ; human LIN-2 PDZ (422–507); human erythroid p55 PDZ (1–164); and human AF-6 PDZ (983–1102). Glutathione beads (50 to 60 μl) saturated with GST-PDZ proteins were mixed with the peptide library (1 mg) in 300 μl of TSN buffer [40 mM triethylamine (pH 7.6), 150 mM NaCl, and 0.01% NP-40] containing bovine serum albumin (BSA, 1 mg/ml) and 1 mM dithiothreitol (DTT). After 45 min of constant shaking at 4°C, the beads were washed with TSN buffer. The peptides retained were eluted with 30% acetic acid, lyophilized, resuspended in distilled water, and sequenced on a Bio-Applied 477A sequencer.
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22 July 1996; accepted 23 October 1996

The Inverse Association Between Tuberculin Responses and Atopic Disorder

Taro Shirakawa, Tadao Enomoto, Shin-ichiro Shimazu, Julian M. Hopkin*

Human immune responses are heterogeneous and may involve antagonism between T helper (T_H) lymphocyte subsets and their cytokines. Atopy is characterized by immediate immunoglobulin E (IgE)–mediated hypersensitivity to agents such as dust mites and pollen, and it underlies the increasingly prevalent disorder asthma. Among Japanese schoolchildren, there was a strong inverse association between delayed hypersensitivity to *Mycobacterium tuberculosis* and atopy. Positive tuberculin responses predicted a lower incidence of asthma, lower serum IgE levels, and cytokine profiles biased toward T_H1 type. Exposure and response to *M. tuberculosis* may, by modification of immune profiles, inhibit atopic disorder.

Atopy is a state of allergic response, mediated by IgE, to largely innocuous, common environmental antigens (allergens) such as those derived from house dust mites and plant pollens (*1*); it underlies the clinical diseases of asthma, hay fever, and eczema (*2*). Atopy can be recognized by allergen-specific IgE in serum or by immediate-type hypersensitivity reactions to allergens upon intradermal skin testing. Heterogeneous genetic and environmental factors interact in the development of atopy (*3*); a set of cytokines—interleukin-4 (IL-4), IL-10, and IL-13 derived from the T_H2 subset of T lymphocytes—is central in mediating IgE production and the development of immediate hypersensitivity (*4*).

In recent decades there has been an increase in severity, and probably in prevalence, of atopic disorders in developed countries (*5*). Studies on migrants from developing to developed countries support the importance of etiological environmental changes associated with "Westernization" (*6*). The nature of these environmental changes is obscure, but speculation has focused on increased air pollution or other toxins in the environment, increased indoor exposure to dust mite antigens in less ventilated modern homes, and dietary changes (*7*). One factor temporally associated with the rise of atopy is the decline of many infectious diseases in developed countries as the result of improved living standards and immunization programs (*8*). Data on the risk of atopy according to sibship size and birth order (*9*) also support the possibility that diminished exposure to infection might, in some way, promote atopic responses. Childhood respiratory infections that might strongly modify the developing immune system, both systemically and within the lung, include measles, whooping cough, and tuberculosis. Some of these infections cultivate a T_H1 immunological environment with IL-12, interferon-γ (IFN-γ), and tumor necrosis factor (TNF) as predominant cytokines (*10*); because these cytokines inhibit T_H2 cytokine functions (*11*), the absence of such infections might release T_H2 immune mechanisms and thus promote atopic disorder.

In the case of tuberculosis, an important marker of T_H1-mediated acquired immunity (not synonymous with protection) is the development of delayed-type hypersensitivity. This can be tested by observing the reaction, after 48 hours, to the intradermal injection of tuberculin protein (*12*). There is likely a "J-shaped" relation between the degree of delayed hypersensitivity and the risk of tuberculous disease, in which people with moderate hypersensitivity are at least risk (*13*).

To test for clinical evidence of antagonism between delayed hypersensitivity to tuberculin and immediate atopic responses, we conducted an epidemiologic survey in a county of the Wakayama prefecture in southern Honshu, Japan, where there has been a long-established program of tuberculin testing and immunization with attenuated bovine *M. tuberculosis* vaccine [bacillus Calmette-Guérin (BCG)] after birth and at 6 and 12 years of age (*14*). From a population of approximately 1000 12- to 13-year-old schoolchildren attending the 18 junior high schools of the county in 1995, we studied 867 children with complete retrospective records of their tuberculin responses. We administered a

T. Shirakawa and J. M. Hopkin, Lung Research Laboratory, Osler Chest Unit, Churchill Hospital, Oxford OX3 7LJ, UK.
T. Enomoto, Department of Otolaryngology, Japanese Red Cross Society, Wakayama Medical Center, Wakayama, Japan.
S. Shimazu, Department of Pediatrics, National Wakayama Hospital, Wakayama, Japan.

*To whom correspondence should be addressed. E-mail: jhopkin@immsvr.jr2.ox.ac.uk

questionnaire documenting atopic symptoms and social and environmental variables, and we also measured IgE serum levels and T_H1 and T_H2 cytokine profiles (*15*); these data were analyzed in relation to the record of tuberculin responses.

There was a bimodal distribution of delayed-type hypersensitivity responses to tuberculin upon skin testing (Fig. 1A). Positive tuberculin tests (≥10 mm skin induration) correspond to response to *M. tuberculosis*; negative tests include fully negative reactions as well as intermediate reactions (5 to 9 mm) that generally reflect responses to nontuberculous environmental mycobacteria or to BCG (*16*). Positive tuberculin responses were recorded in 3% of the children at 3 months of age, in 33.2% at 6 years, and in 58.0% at 12 years. In many children, the tuberculin status changed, to either positive or negative, between the ages of 6 and 12 years (Table 1, groups 2 and 4). None of the children suffered clinical tuberculous disease at any stage, including 24 with florid tuberculin responses (>40 mm skin induration) who underwent full clinical and radiographic assessment for the disease.

Of all the children studied, 36% manifested atopic symptoms at some time. A strong inverse association was found between positive tuberculin responses at both 6 and 12 years of age and a range of atopic characteristics, including symptoms at any age and IgE levels and T_H2 cytokine profiles assayed at 12 years of age (Fig. 1B and Tables 1 and 2). In positive tuberculin responders, the rate of current atopic symptoms was one-third the rate in negative responders. Asthmatic symptoms were one-half to one-third as likely in positive tuberculin responders as in negative responders (Table 2). Moreover, remission of atopic symptoms between 7 and 12 years of age was six to nine times as likely in positive tuberculin responders. Serum IgE levels, both total and allergen-specific, were also lower in the positive tuberculin responders. The geometric mean for total serum IgE level was 112

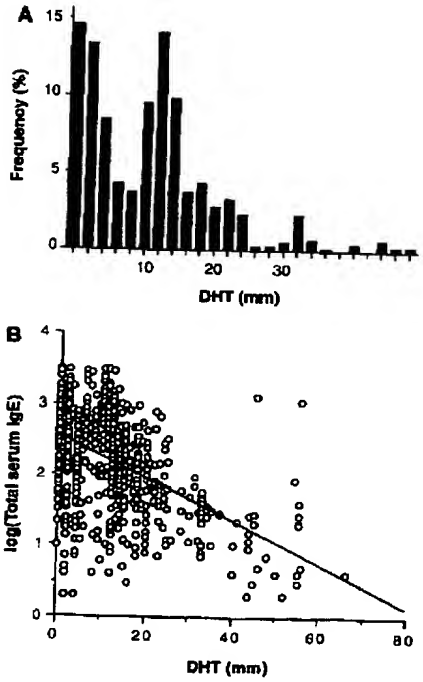

Fig. 1. Delayed hypersensitivity to tuberculin (DHT, in millimeters) and relation to serum IgE. (**A**) Histogram showing bimodal distribution of responses to tuberculin, assayed as DHT at 12 years of age in 867 Japanese schoolchildren. (**B**) Plot of log(total serum IgE) versus DHT in the same children ($r = -0.492$, $P < 0.001$).

Table 1. History of infectious diseases, atopic symptoms, IgE levels, and cytokine profiles in subjects grouped by tuberculin reactivity. ASE, allergen-specific IgE; UD, undetectable.

Measurement	Group 1 (n = 290)	Group 2 (n = 289)	Group 3 (n = 213)	Group 4 (n = 75)	Total (n = 867)
Tuberculin response					
At 6 years	−	−	+	+	
At 12 years	−	+	+	−	
Positive antiviral immunity (%)					
Measles (history + vaccine)	83.4	87.2	84.5	81.3	84.3
Chicken pox (history + vaccine)	86.9	82.3	82.2	82.7	83.9
Mumps (history + vaccine)	62.8	60.9	60.1	57.3	61.0
Number with IgE to *Ascaris*	2	2	2	1	7
Symptoms (%)					
Atopy (past + present)	46.8	33.9‡‡	25.8‡‡	38.7	36.6
Atopy (present)	32.1	7.9‡‡‡	9.8‡‡‡	30.7	18.5
Asthma (past + present)	13.4	4.1‡‡	3.7‡‡	6.8	7.4
Rhinitis (past + present)	16.2	4.8‡‡	8.6‡	14.6	10.4
Eczema (past + present)	22.7	12.8‡‡	12.2‡‡	16.0	16.2
Geometric mean IgE (IU/ml)	208	149**	98***	178	154
Positive ASE (%)	55.8	43.9‡‡	41.8‡‡	53.3	48.2
Atopic (high IgE or positive ASE) (%)	65.5	54.0‡‡	49.2‡‡	61.3	57.3
Median cytokine level (pg/ml)					
IL-4	1.88	0.96†	0.92†	1.66	1.22 (10.2-UD)§
IL-13	18.3	10.2†††	7.8†††	19.1	14.2 (45.6-UD)
IL-10	5.9	3.1††	2.9††	5.9	3.9 (10.2-UD)
IL-12	UD	UD	UD	UD	UD
IFN-γ	7.8	11.0††	13.2††	6.4	10.5 (23.2-UD)
Positive family history within three generations (%)	54.1	49.8	49.8	48.0	51.0
Mean BMI	21.1	22.0	21.9	21.2	21.6

**$P < 0.01$, ***$P < 0.001$ on the basis of Student's test. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ on the basis of a median test. ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$ on the basis of χ^2 against group 1, respectively. §Maximum-minimum values.

Table 2. Odds ratios for atopy and for occurrence and remission of atopic symptoms in positive versus negative tuberculin responders by age. Multiple logistic analysis was conducted with the SPSSX package, version 2.2. In all models, allowance was made for dichotomized variables including sex, life-style, nutritional status, environmental factors, and family history. Only significant values are shown.

Tuberculin response	Odds ratio		
	Atopy	Atopic symptoms	
		Occurrence	Remission
Conversion to positive up to 6 years of age	0.50 (0.29 to 0.83)*	Asthma: 0.31 (0.22 to 0.45)* Eczema: 0.50 (0.33 to 0.91)*	Asthma: 8.2 (6.0 to 9.8)** Eczema: 1.6 (1.0 to 2.2)*
Conversion to positive between 6 and 12 years of age	0.43 (0.25 to 0.83)**	Asthma: 0.42 (0.24 to 0.56)*	Asthma: 6.0 (2.8 to 10.3)*** Eczema: 6.7 (4.8 to 11.4)*** Rhinitis: 9.0 (6.2 to 14.2)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$.

IU/ml for children who had a positive tuberculin response at any time, whereas it was 194 IU/ml for children whose responses were always negative. A plot of the logarithm of total serum IgE against the diameter of tuberculin response shows an inverse linear relation, $r = -0.492$ (Fig. 1B). Positive tuberculin responders had significantly lower levels of T_H2 cytokines (IL-4, IL-10, and IL-13) and higher levels of the T_H1 cytokine IFN-γ.

In tests for confounding variables (*15*), we found no differences in life-style, environmental factors, or nutritional status between the positive and negative tuberculin responders; estimated allergen exposure was similar among the groups with respect to pet animal exposure, character and ventilation of homes, and residence in a rural area. Exposure to helminths, which can promote high IgE levels, was minimal in the population; only 7 of the 867 children showed IgE to *Ascaris lumbricoides*. Similar numbers of positive and negative tuberculin responders reported atopy in any sib, parent, or grandparent (~50%) or had chest radiograph reports of tuberculosis in the same relatives at any time (~13%).

Several lines of evidence suggest that a causal link between tuberculin response and atopy is more likely than fixed determination of both atopy and diminished tuberculin responses by a genetic factor or factors. Our data show that tuberculin responses change, from positive to negative and vice versa, in many children between 6 and 12 years of age (groups 2 and 4 in Table 1). A marked decline in the incidence of positive tuberculin responses in the Wakayama region over a very short genetic interval—95% in 1965, 85% in 1975, 60% in 1985, and 58% in our survey—was accompanied by a decline in infectious clinical cases of tuberculosis from 154.4 per 100,000 in 1974 to 52.1 per 100,000 in 1994 (*17*). Experimental animal data show antigen-independent, reciprocal inhibition of either T_H1 or T_H2 immunity by infectious agents that strongly promote T_H1 responses [such as mycobacteria (*18*)] or T_H2 responses [such as schistosomes (*19*)]. The data support the hypothesis that a decline in infection, in this instance tuberculosis, is a factor underlying the rising severity and prevalence of atopic disorders in recent decades in developed countries. These data are also consistent with the idea that atopic responses are limited by T_H1 immune mechanisms.

Epidemiological data from Guinea-Bissau show that a history of childhood measles infection around the time of an epidemic was associated with a 50% decrease in the rate of positive atopic skin tests (*20*). In our study, we found no relation between a history of measles infection and atopy. However, there are important population and environmental differences between Wakayama and Guinea-Bissau; also, the Wakayama region has had an established program of measles immunization, with an uptake of 60% or more, and there had been no measles epidemic relevant to our study. It is likely that a set of specific infections that strongly promote T_H1 immunity has the potential to inhibit atopic disorder by the repression of T_H2 immunity. We believe that the role of such an infection in repressing atopy depends on a number of factors, including its timing, anatomical site, dose, and protractedness; exposure to other infections; and host characteristics such as genetic variables and nutritional status (*21*). Prospective and experimental studies are needed to investigate the action of *M. tuberculosis* and other microorganisms, through natural infection or immunization schedules, in deviating immunity away from atopy.

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Early BCG vaccination and development of atopy

Johan S Alm, Gunnar Lilja, Göran Pershagen, Annika Scheynius

Summary

Background The increase in atopic diseases may be partly explicable by a decline of certain infectious diseases, or changes in childhood vaccination programmes, or both. We investigated whether BCG vaccination against tuberculosis influences the development of atopy.

Methods We did a retrospective cohort study of 216 children with atopic heredity, born in Stockholm between 1989 and 1992, who received BCG vaccination when they were younger than 6 months, and 358 age-matched controls who had not been vaccinated. Both groups attended Sachs' Children's Hospital, Stockholm, Sweden, during 1995–96 for assessment of atopic history and clinical signs of atopic disease. All children also underwent skin-prick testing (SPT) and serum was analysed for allergen-specific IgE antibodies. Serum from parents was also analysed for IgE antibodies.

Findings 77 (36%) children in the BCG group and 145 (41%) in the control group had a positive history or clinical signs of atopic disease. In the vaccinated group, 26 (12%) children had one or more positive SPT, and 61 (31%) had circulating allergen-specific IgE antibodies, whereas in the control group, the numbers were 35 (10%) and 84 (27%) respectively. Atopy was confirmed by serology in parents of almost two-thirds of the children in each group. Other risk factors for atopic disease were evenly distributed between the two groups.

Interpretation early BCG vaccination in children with atopic heredity does not seem to affect the development of atopic disease before school age.

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Sachs' Children's Hospital (J S Alm MD, G Lilja MD); **Division of Environmental Epidemiology, Institute of Environmental Medicine** (Prof G Pershagen MD), **and Division of Clinical Immunology, Department of Laboratory Medicine** (J S Alm, Prof A Scheynius MD), **Karolinska Institute and Hospital, S-171 76 Stockholm, Sweden**

Correspondence to: Dr Johan S Alm

Introduction

The occurrence of atopic disease mediated by IgE antibodies is increasing in developed countries, and the proportion of children with asthma, atopic dermatitis, rhinoconjunctivitis, or food allergy, is now more than 30%.[1–3] The reasons for this increase are largely unknown, but environmental factors are thought to have an important role. For example, associations with residence in industrial or urban areas and a western lifestyle have been found in comparisons of eastern and western Europe.[3,4]

T-helper (Th) lymphocytes have a central regulatory influence on allergic inflammation and can be subdivided according to their production of cytokines.[5] Th1 cells, when stimulated with virus or intracellular bacteria, secrete interferon-γ, which can inhibit IgE production by B cells.[5,6] By contrast, Th2 cells, when stimulated with allergens or parasites, release interleukin-4, which promotes IgE production by B cells.[5,6] Th2 activity dominates in atopic individuals.[6]

BCG vaccine is a potent adjuvant for induction of cell-mediated immunity[7] and induces interferon-γ as one

of the major cytokines.[8] This action may cause a Th1-activity type immune response.[8] BCG vaccine has been used in attempts to modulate the immune response and, thereby, interfere with the pathogenesis of diseases. Studies in diabetes-prone mice have shown that a single injection of BCG vaccine given at an early age can prevent the development of type 1 diabetes.[9,10] In a trial of children with newly diagnosed type 1 diabetes, a single intracutaneous dose of BCG vaccine led to long-term clinical remission.[10]

The increase in atopic disease may be partly explained by a decline in certain infectious diseases, as well as changes in immunisation programmes. BCG vaccine was given to 95% of all newborn babies in Sweden until 1975, when vaccination was stopped because of side-effects and lower risk of tuberculosis exposure.[11] Vaccination is now offered only to high-risk groups, such as children who have a close relative with tuberculosis or immigrants from some areas, or upon parental request. Therefore, the vaccination rate is now less than 4% in Swedish-born children.[11] We assessed the influence of BCG vaccination in early life on the development of atopy in children with atopic heredity.

Methods

780 children born between 1989 and 1992 who received BCG vaccination before the age of 6 months were traced from Child Welfare Centre records in the catchment area of Sachs' Children's Hospital in south Stockholm (table 1). In this area, 99·7% of all families with infants visited the Child Welfare Centres.[12] Nurses at these centres were asked to exclude children of non-Nordic parents to keep potential confounding to a minimum. A questionnaire about atopic disease among the parents was sent to all these families. 650 (83%) of 780 responded, and 283 of these children had no atopic heredity. Among the remaining children, 87 who had been vaccinated after the age of 6 months were excluded, and 37 refused further participation, which left 243 children for clinical assessment.

A control group of children, age-matched by calendar year, was randomly selected from population registers among children living in the same area as the BCG group. After exclusion of non-Nordic infants, 1266 children remained. The control group received the same questionnaire as the BCG group. 980 (77%) replies were received (table 1). The parents of 475 of these infants reported no atopic symptoms. Among the remaining children, 40 were excluded because of previous BCG vaccination, and 73 refused further participation. Therefore, the control group consisted of 392 infants.

The parents of both groups of infants were mailed a second questionnaire about atopic symptoms as well as social and environmental details, and were asked to visit the outpatient ward at Sachs' Children's Hospital, Stockholm, Sweden, between October, 1995, and October, 1996, for a clinical assessment. At this point, in the BCG group consisting of 243 children (87% of those invited), two children had no vaccination scar, 11 had had late (>6 months) BCG vaccination, and 21 had non-Nordic parents. These 34 infants were excluded from further study, which left 209 infants. Seven controls had been vaccinated before the age of 6 months, and these were transferred to the BCG group, and, therefore, the BCG group consisted of 216 children after clinical assessment.

The mean age at BCG vaccination was 17 days (range 0–180) for girls (n=104), and 21 days (range 1–173) for boys (n=112). In the control group, 392 (84%) children were clinically assessed. After further exclusion of eight infants who were vaccinated at older than 6 months and 19 who had non-Nordic parents, 358 children remained in this group (172 girls and 186 boys). The mean age at examination was 5·5 years (range 3·1–7·2) and 5·4 years (range 2·9–7·2) in the BCG and control groups, respectively.

	BCG group	Control group
Screening stage		
Selected for screening	780	1266
Responded to screening questionnaire	650 (83%)	980 (77%)
Atopic heredity by history	367	505
Excluded because of late vaccination (>6 months)	87*	40*
Clinical assessment		
Invited	280	465
Attended	243 (87%)	392 (84%)
No visible BCG scar	2*	377
Late vaccination (>6 months)	11*	8*
Non-Nordic parent	21*	19*
BCG-vaccinated controls transferred to BCG group	7	..
Final study groups	216	358

*Excluded.

Table 1: **Selection of children with early BCG vaccination and controls**

All clinical assessments were done by the same doctor (JSA) who was not aware of the vaccination status or test results. The clinical diagnosis of atopic disease was based on information from the questionnaire and from the clinical assessment. The following criteria were used.

Bronchial asthma—three or more episodes of wheezing before the age of 2 years, or one episode at 2 years or older, or any episode of wheezing, independent of age, if combined with familial atopy or other atopic symptoms in the child.

Allergic rhinoconjunctivitis—rhinitis, or conjunctivitis, or both, at least twice after exposure to a particular allergen, and unrelated to infection.

Food allergy or allergic urticaria—acute onset of symptoms such as skin reactions, wheezing, vomiting, or diarrhoea on more than one occasion after ingestion or contact with a particular type of food or allergen.

Atopic dermatitis—as described by Hanifin and Rajka.[13]

The BCG vaccine used was attenuated Kb 1331 strain of *Mycobacterium bovis*, without preservative (Statens Seruminstitut, Copenhagen, Denmark).[11] In children younger than 1 year, this vaccine is given as 0·05 mL intracutaneously on the proximal

	BCG group (n=216)	Control group (n=358)
Clinical symptoms or history of atopic disease		
Bronchial asthma	22 (10%)	43 (12%)
Atopic dermatitis	58 (27%)	107 (30%)
Allergic rhinoconjunctivitis	31 (14%)	34 (9·0%)
Food allergy	6 (3·0%)	7 (2·0%)
Urticaria	10 (5·0%)	9 (3·0%)
Total with at least one symptom	77 (36%)	145 (41%)
Skin-prick test		
≥1 positive test	26 (12·0%)	35 (10%)
Cat	10 (4·8%)	13 (3·8%)
Dog	2 (1·0%)	2 (0·6%)
Horse	4 (1·9%)	7 (2·0%)
Birch	7 (3·3%)	12 (3·5%)
Timothy grass	6 (2·9%)	5 (1·5%)
Mugwort	0	0
Cladosporium	0	0
D pteronyssinus	1 (0·5%)	0
Peanut	7 (3·3%)	10 (2·9%)
Egg white	2 (1·0%)	1 (0·3%)
Codfish	0	2 (0·6%)
Cow's milk	1 (0·5%)	0
Soy bean	1 (0·5%)	0
Number tested	210 (97%)	344 (96%)
Blood sample from children		
Any serology positive	61 (31%)	84 (27%)
Phadiatop positive only	20 (10%)	31 (10%)
fx5 positive only	17 (9%)	31 (10%)
Phadiatop and fx5 positive	24 (12%)	22 (7·0%)
Total with blood samples available	194 (90%)	317 (89%)

Table 2: **Signs of atopy according to clinical examination, SPT, and serological tests in children with early BCG vaccination and controls**

lateral part of the left upper arm without a previous tuberculin test.[14] None of the children received a subsequent tuberculin test or revaccination. All children in the final BCG group had a scar at the site of vaccination, which was confirmed in the clinical assessment.

Skin-prick tests (SPT) (Soluprick, ALK, Copenhagen, Denmark) were done on the volar side of the child's lower arm. These included tests for birch, cat, cladosporium, *Dermatophagoides pteronyssinus*, dog, horse mugwort, and timothy grass (10 HEP), hen's-egg white (1/100 weight/volume), codfish (1/20), cow's milk (3% fat, standard foodstuff), peanut (1/20) and soy bean (Soja Semp, Semper AB, Stockholm, Sweden). Histamine chloride 10 mg/mL was used as the positive control and the allergen diluent as the negative control. An SPT was deemed positive if the weal was at least 3 mm in diameter and larger than or equal to the histamine-induced weal after 15 min. The same batches of each extracts were used and the SPTs were done throughout the study by the same nurse who was unaware of vaccination status.

A capillary blood sample was taken from each child and from the parent with the most probable atopic history. The blood samples were centrifuged and serum was separated and stored at −20°C until analysis, which included detection of circulating IgE antibodies (Pharmacia Diagnostics AB, Uppsala, Sweden) against 11 common inhalant allergens (Phadiatop) and six food allergens (fx5). Infants with at least one positive SPT to any of the selected food or inhalant allergens, or a positive Phadiatop, or a positive fx5, or any combination, were classed as atopic.[11]

Data were analysed by χ^2 tests or Fisher's exact test (mid p values) to compare proportions; for continuous data, the Mann-Whitney non-parametric *U* test was used. Significance was set at $p<0.05$. Power calculations were done according to Casagrande and colleagues' calculations.[16]

The study was approved by the local research ethics committee, and informed consent was given by all parents.

Results

Positive history or clinical signs consistent with atopy were seen in 36% of the BCG group and in 41% of controls, of which the youngest were 19 months (range 0–51) and 24 months (1–72), respectively (table 2). The distribution of different atopic symptoms in the two groups did not differ significantly.

12% of infants in the BCG group had positive SPT reactions compared with 10% of controls, with an equal distribution for different allergens between the two groups (table 2). A positive reaction to cat antigens was most common, followed by birch, peanut, timothy grass, and horse.

Blood samples were available for nearly 90% of children (table 2). In the BCG group, 10% had positive Phadiatop tests and 9% had positive fx5 tests. The corresponding proportions in the control group were 10% for both tests. A greater proportion of the BCG group than of the control group had positive results in both in-vitro tests (12 *vs* 7%), but overall, the percentage of positive results was similar in the two groups. When results from STP and serological tests were combined, the rate of atopy according to Pepys' definition[15] was 29% and 24% in the BCG group and the control group, respectively.

Demographic data and risk factors for atopic disease are presented in table 3. There were no clear differences between the BCG group and controls in birthweight (mean 3544 g and 3473 g), gestational age at birth (39·9 and 39·7 weeks), number of children in the family (2·2 in both groups), or other risk factors for atopic disease, such as heredity, sex, short duration of breastfeeding, parental smoking, and furred pets in the home. Parental atopy was verified by serology in 63% and 66% of parents in the BCG and control groups, respectively (table 3). Restriction of the analysis to the children of these parents did not result in significant differences between the groups for any outcome (data not shown).

	BCG group (n=218)	Control group (n=358)
Characteristics of children		
M/F	108 (52%)/104 (48%)	186 (52%)/172 (48%)
Low birthweight (<2500 g)	4 (3·2%)	11 (3·1%)
Breastfed exclusively ≥4 months	124 (57·0%)	226 (63·0%)
Characteristics of home		
Maternal tobacco smoker (≥1 cigarette/day)	53 (25%)	93 (26%)
Live in flat	108 (50%)	166 (46%)
Furred pets in household	101 (47%)	147 (41%)
Moisture inside window panes at home	11 (5·0%)	15 (4·2%)
Family history of atopy		
Mother	76 (35%)	120 (33%)
Father	56 (26%)	99 (28%)
Both parents	84 (39%)	139 (39%)
Blood samples from parents	200 (93%)	337 (94%)
Positive atopy serology in parents	125 (63%)	221 (66%)
Origin of parents*		
Denmark	1	3
Finland	28	17
Norway	0	4
Total	29 (13·0%)	24 (6·7%)

*Other than Sweden

Table 3: **Demographic data and risk factors for atopic disease in the BCG group and controls**

Based on the proportions in the control group, the statistical power of the study to detect a 50% reduction in frequency of atopy was 99% for clinical symptoms or history of atopic disease, 48% for at least one positive SPT, and 89% for any positive serology.

Discussion

This study shows that early BCG vaccination has no primary preventive effect on the development of atopic disease before school age in children with atopic heredity. To increase the efficiency of our study, only children whose parents had a history of atopy were included. The statistical power was adequate to detect a 50% reduction in the frequency of clinical or serological signs of atopy among the children in the BCG group. The occurrence of clinical symptoms of atopy, and the frequency and distribution of positive SPTs and positive serological tests in the two groups are similar to those in other Swedish studies of children of similar age and with atopic heredity.[17,18] The clinical part of the study was masked to reduce the risk of exposure-related misclassification of the outcomes. Non-response rates were similar for children who were and were not vaccinated and the occurrence of atopy is unlikely to differ greatly between the non-responders in the two groups. The distribution of risk factors for development of atopic disease was similar among the BCG group and controls, which reflects a lack of confounding by these factors. The distribution of risk factors was also similar to that found in other Swedish studies.[19,20] A higher proportion of the BCG-group parents were born in Nordic countries other than Sweden, but most of these parents came from Finland, where the atopy rates are similar to those in Sweden.[17,21]

The protective efficacy of BCG vaccine against tuberculosis is debated.[22] Mantoux skin testing is the established method of checking the protection, although

the correlation is doubtful because of individual differences in the reactivity to tuberculin[14,23] and cross-reactions to atypical mycobacteria.[14] The presence of a scar is thought to be the best sign of a successful vaccination[14] and we used scars to confirm vaccination in our study.

Shirakawa and colleagues[24] reported that positive tuberculin responses among Japanese schoolchildren aged 12–13 years correlated with a lower incidence of atopic disorders. Positive tuberculin responses (≥10 mm skin induration) were recorded in 3% of the children at age 3 months, 33% at age 6 years, and 58% at age 12 years. At each of these ages, negative responders were BCG vaccinated. The rate of atopic symptoms was significantly lower in children with positive tuberculin reactions. Much of the inverse association between tuberculin and atopy was due to children with strong tuberculin responses (>40 mm skin induration). An important difference between the children in the Japanese study and ours, apart from different vaccination programmes, is the environmental exposure to mycobacteria. The incidence of tuberculosis is about ten times higher in Japan than in Sweden.[24,25] Natural exposure to mycobacteria but also a predisposition in the individual to a Th1 response may have implications for the interpretation of the Japanese results. The difference in outcome after vaccination and natural infection is illustrated in a retrospective cohort study from Guinea-Bissau, where measles infection, but not childhood measles vaccination, was associated with a reduction in atopy.[26] How the immunological responses to a measles infection and vaccination differ is not clear,[27,28] but a protective effect against atopy was achieved only by real infection.

Early BCG vaccination in infants with atopic heredity seems to have no significant effect on the devlopment of atopic disease before school age. If these findings are the same for older children and children without atopic heredity, vaccination may not constitute an effective primary preventive strategy for atopic diseases.

Contributors

Johan S Alm, Gunnar Lilja, Göran Pershagen, and Annika Scheynius were all involved in the planning of the study, data analysis, and manuscript preparation. The clinical part of the study was done by Johan S Alm. Paediatric allergology was dealt with by Gunnar Lilja. Göran Pershagen was responsible for matters related to epidemiology. Matters related to immunology were dealt with by Annika Scheynius.

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ARTICLE

A Randomized Controlled Trial of the Effect of Pertussis Vaccines on Atopic Disease

Lennart Nilsson, MD; N.-I. Max Kjellman, MD, PhD; Bengt Björkstén, MD, PhD

Background: Pertussis vaccination in infancy has been suggested to increase the risk for development of asthma and allergy.

Objective: To assess sensitization rates and development of atopic diseases in a prospective randomized controlled trial of pertussis vaccine.

Patients and Methods: A total of 669 children were randomized to 1 of 4 vaccine groups (2-component acellular pertussis, 5-component acellular pertussis, whole-cell pertussis vaccines, and placebo [diphtheria and tetanus toxoids]). Diphtheria and tetanus toxoids were also given to the children in the pertussis vaccine groups. The children were evaluated by means of questionnaires at age 2 months, 7 months, and 2½ years; skin prick tests at age 7 months and 2½ years; and blinded clinical investigation at age 2½ years. The families were contacted at regular intervals to assess possible adverse effects after the vaccinations and symptoms of whooping cough.

Results: The cumulative incidence of atopic diseases was 30% and incidence rates were similar in the 4 groups after adjusting for family history. Exposure to environmental tobacco smoke and home dampness did not confound these results. The frequency of adverse effects did not differ appreciably between atopic and nonatopic children, with the exception that a nodule at the vaccination site was more frequent after whole-cell pertussis vaccination in the nonatopic children. Among 47 children with proven pertussis, atopic disease appeared in 19 (40%). Of these 47 children, 9 (19%) developed asthma, as compared with 58 (9%) noninfected children ($P = .03$).

Conclusions: We found no support for a drastic increase in allergic manifestations after pertussis vaccination. There was a positive association between whooping cough and asthma by 2½ years of age. There seems to be little reason to withhold pertussis vaccination from infants, irrespective of family history of allergy.

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Editor's Note: This study should help to allay fears of increased atopy with pertussis vaccine; in fact, if that was the reason you used not to immunize, the data on atopy following pertussis vaccination should stimulate you to do so.

Catherine D. DeAngelis, MD

THE ETIOLOGY of asthma and allergy is multifactorial and a consequence of an interaction between genetic susceptibility and environmental factors, particularly those encountered early in life.[1,2] Tobacco smoke is a major adjuvant factor for the development of asthma and allergy; avoidance of environmental tobacco smoke is essential in both primary and secondary prevention.[3] Other potential adjuvants include certain infections and vaccinations.[1] *Bordetella pertussis* may be particularly important in this respect, as judged from experiments in animals[4-7] and experiences in humans.[8-12]

In children, IgE antibodies to pertussis toxin are commonly found after infection and immunization.[12] It was recently suggested that whole-cell pertussis vaccination in infancy may increase the risk of asthma 5-fold, from 2% to more than 10% during childhood.[11] However, in a study of nearly 10 000 children, a questionnaire survey with 3 questions on allergy symptoms did not support these findings.[13] As part of a study of the efficacy of 3 pertussis vaccines, we prospectively studied the development of atopic disease and sensitization during the first 2½ years of life in relation to type of vaccine and possible confounders, including the effect of pertussis infection. Adverse effects related to pertussis vaccination were also considered, to evaluate both advantages and disadvantages of pertussis immunization.

From the Division of Pediatrics, Department of Health and Environment, Faculty of Health Sciences, University Hospital, Linköping, Sweden.

RESULTS

Atopic disease was verified in 201 children (30%) during the first 2½ years of life. Atopic dermatitis occurred in 140 children (21%), and 67 children (10%) had bronchial asthma. Allergic rhinoconjunctivitis was found in 14 (2%), urticaria in 15 (2%), and food allergy in 12 (2%) of the children. Ninety-one children (14%) had a positive SPT to at least 1 allergen at 7 months of age. The prevalence of positive SPTs decreased with older age, as only 63 children

PATIENTS AND METHODS

PATIENTS

In a Swedish pertussis vaccine trial of 9829 children at 14 study centers, 788 infants in Linköping, Sweden, were randomized to a double-blind comparison of the effects of 2-component acellular pertussis vaccine (2-c, SmithKline Beecham, Rixensart, Belgium), 5-component acellular pertussis vaccine (5-c, Connaught Ltd, Toronto, Ontario), whole-cell pertussis vaccine (WC, Connaught Laboratory Inc, Swiftwater, Pa), and diphtheria and tetanus toxoids vaccine (DT, Swedish National Bacteriological Laboratory, Stockholm) used as placebo.[14] The families of 711 infants also agreed to be included in the allergy study and 699 infants received 3 doses of vaccine as scheduled. The 2-c vaccine was given to 188 children, 184 received the 5-c vaccine, 143 the WC vaccine, and 184 children received only DT. In all, 17 families moved from the area, and 6 families decided to withdraw during the study period, and 7 children had incomplete follow-up data, leaving 669 children who were followed up from 2 months up to 2½ years of age. The demographics of the 30 children who were unavailable for follow-up did not differ significantly from that of the remaining children.

The children received their first vaccine dose in the trial at age 2 months (56-92 days), and were evaluated at age 7 months (1 month after dose 3), and at about age 2½ years (mean, 2 years 5 months; range, 2 years 3 months to 2 years 8 months). The parents received questionnaires regarding tobacco smoke exposure of the children, home dampness (defined as problems in the house, such as leaking pipes or condensation on 2-glass window panes at temperatures below 0°C), pets in the house, type of feeding, and possible allergic symptoms in the children at 7 months and at 2½ years of age. The questions regarding symptoms in the skin, nose, and bronchi (**Figure 1**) were modified from the International Study of Asthma and Allergies in Childhood ("ISAAC") questionnaires.[15]

Skin prick tests (SPTs) were performed in duplicate on the volar aspect of the forearm with milk, egg white, and cat dander antigens at 7 months (n = 669), and with egg, cat dander, dog dander, 2 mites (*Dermatophagoides pteronyssinus* and *D farinae*), and timothy and birch antigens at 2½ years of age (n = 666). Undiluted cow's milk and hen's egg and Soluprick SQ extracts (10 HEP; Allergologisk Laboratorium A/S, Hørsholm, Denmark) for other allergens were used according to the recommendations by the European Academy of Allergy and Clinical Immunology.[16] Tests were regarded positive if skin wheals had a mean diameter of 3 × 3 mm or more after 15 minutes. Histamine dihydrochloride, 10 mg/mL, and blank lancets were included as positive and negative controls. No antihistamine should have been used during 3 days preceding the SPT.

Physical examinations and, if needed, additional tests, were performed at 2½ years of age and when bronchial asthma or allergy was suspected by the study nurses.

The parents of all participating children gave their informed consent. The study was approved by the Human Research Ethics Committee of the Medical Faculty at the University of Linköping.

DIAGNOSTIC CRITERIA

The diagnoses were made on the basis of questionnaires, clinical findings, and information in medical records. Bronchial asthma was defined as at least 3 episodes of obstructive bronchitis before 2 years of age or 1 episode of bronchial obstruction after 2 years of age in the absence of other explanations. Atopic dermatitis was defined as persisting or recurring itching eczema for 6 months or more. A child was regarded as having allergic rhinoconjunctivitis in the case of an affirmative answer to both of the following questions: "Has your child, during the last 12 months, suffered from sneezing, rhinorrhea, or blocked nose without having a cold?" and "Have the nose complaints, during the last 12 months, been accompanied by itching or running eyes?" Urticaria was defined as allergic if appearing after exposure to a particular allergen and with a positive SPT to the same allergen. The diagnostic criteria for food allergy included diarrhea, vomiting, urticaria, or Quincke edema after ingestion of a specific food at least once, and demonstrable IgE antibodies to the same food.

The diagnosis of pertussis (whooping cough) was used according to criteria established by the World Health Organization.[17] The families were contacted by telephone every 6 weeks. Blood samples for serological analyses and nasopharyngeal cultures for *B pertussis* were made after 7 days of coughing. A case of pertussis was defined as the presence of paroxysmal cough for at least 21 consecutive days *plus* 1 of the following criteria: isolation of *B pertussis* in culture, an increase of 100% or more in IgG or IgA antibodies against pertussis toxin, an increase of 100% or more in IgG or IgA antibodies against filamentous hemagglutinin (in the absence of positive results for *Bordetella parapertussis* on culture or polymerase chain reaction analysis), or documented contact with an infected household member with culture-confirmed *B pertussis* infection who began to cough within 28 days before or after the onset of cough in the study child.

The investigation was blinded to the families, nurses, and investigating physicians through the use of coded bottles until the diagnoses were established in all the children.

STATISTICAL ANALYSIS

Statistical comparisons were made using χ^2 tests and Fisher exact tests. Adjustments for differences in family history of atopic disease were performed in the main comparisons between study groups using a logistic regression model (version 3.1 of JMP, SAS Institute Inc, Cary, NC). Study group differences were taken into account by introducing indicator variables, as were differences in family history. An additive model containing such indicators seemed to be adequate and was used.

Sample sizes gave approximately an 80% chance of detecting a 50% treatment group increase above the control group level of atopic diseases during the first 2½ years of age when using a 1-sided test of significance at the 5% level.[18] As the main purpose of the study was to detect considerable increases in the risk of atopic disease by pertussis vaccination, 1-sided tests and 1-sided confidence limits that delimit the increase in risk in an upward direction were used.

(9%) had a positive SPT at 2½ years of age ($P = .02$). At least 1 positive SPT was recorded in 17% of the children, the most common reaction being to egg white, both at 7 months (80/669 [12%]) and at 2½ years of age (41/666 [6%]). A family history of allergy was associated with an increased prevalence of positive SPTs at 7 months of age. Thus, 26 (9%) of 279, 46 (15%) of 308, and 19 (23%) of 82 children with no, single, and double parental history, respectively, had

1. Has your child *ever* had wheezing or whistling in the chest? No/Yes
2. Has your child had wheezing or whistling in the chest at any time during the last 12 months? No/Yes
3. How many episodes with wheezing has your child had during the last 12 months? None/1-3/4-12/>12
4. During the last 12 months, how often, on average, has your child been disturbed by wheezing? Never/Less than 1 night per week/1 or more nights per week
5. During the last 12 months, has the wheezing of your child ever been so severe that he or she only could say 1 to 2 words between the breathings? No/Yes
6. During the last 12 months, has your child had wheezing in the chest during or after exercise? No/Yes
7. During the last 12 months, has your child had dry cough in the nights without having a cold or an infection? No/Yes
8. Has your child ever had wheezing at any time after 2 years of age? No/Yes
9. Has your child ever had 3 diagnosed episodes of bronchitis before 2 years of age? No/Yes
10. Has your child ever had treatment with inhaled Lomudal (cromolyn sodium) or inhaled steroids? No/Yes
11. Has your child ever had a diagnosis of bronchial asthma according to a physician? No/Yes

Figure 1. *Questions for a diagnosis of bronchial asthma. Boldface items indicate responses supporting the diagnosis. A cumulative diagnosis of "bronchial asthma" by 2½ years of age in 67 children was based on a confirmative answer to the following questions: question 1 and one or more of questions 3, 4, 5, 6, and 7 and one or both of questions 8 and 9 (n = 56); question 1 and at least question 11 and confirmed by the medical record of the child (n = 5); question 1 and at least question 8, 9, or 10 and confirmed by the medical record of the child (n = 5); question 11 and confirmed by the medical record of the child (n = 1).*

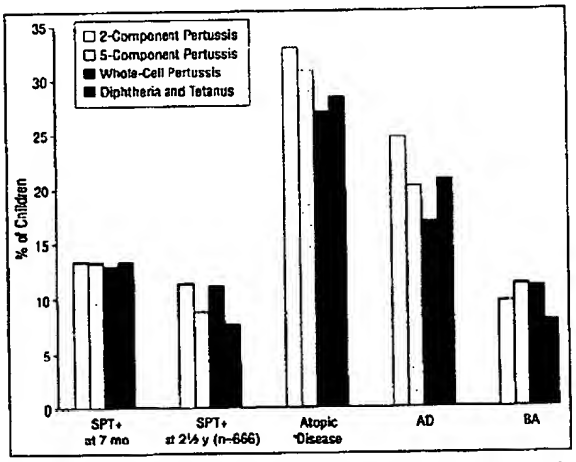

Figure 2. *Atopic manifestations in 669 children during the first 2½ years of age in relation to type of pertussis vaccine. No significant differences were seen between the vaccine groups. AD indicates atopic dermatitis; BA, bronchial asthma; and SPT+, positive skin prick test.*

a positive SPT (P = .004). The corresponding figures for a positive SPT at 2½ years were 8%, 9%, and 19% depending on heredity (P = .02). The cumulative incidence of atopic manifestations was similar in children with a maternal and paternal history of atopic disease (36% vs 37%).

The cumulative incidence of atopic disease at 2½ years of age, as well as the individual manifestations, were similar in the 3 pertussis vaccine groups and the DT group (**Figure 2**). The cumulative incidence of positive SPTs at 7 months and 2½ years of age did not differ significantly between the groups (Figure 2). Using unadjusted data, a positive SPT at 2½ years was found in 12% of the children who had received the 2-c vaccine, as compared with 8% in the DT group (P = .20). Similarly, atopic dermatitis was

Table 1. Demographic Data of 669 Children Immunized With 3 Injections of 1 of 3 Pertussis Vaccines or Placebo*

	Vaccine Group Assignment, % of Children			
Demographic Features	2-c (n = 182)	5-c (n = 178)	WC (n = 137)	DT (n = 172)
Family history of allergy	59.9	62.4	58.4	52.3
Maternal asthma	7.7	8.4	13.9	8.1
Paternal asthma	9.9	7.9	5.1	10.5
Smoking mother	18.7	15.8	19.0	18.7
Smoking father	15.4	18.9	13.1	17.5
Dampness at home	14.3	12.4	13.1	14.0
Pet at home	28.0	24.2	19.0	27.3
Male sex	57.1	50.6	55.5	52.9

**No significant differences were found between vaccine groups (χ^2 test). 2-c indicates 2-component acellular pertussis vaccine; 5-c, 5-component acellular pertussis vaccine; WC, whole-cell pertussis vaccine; and DT, diphtheria and tetanus toxoids vaccine (used as placebo).*

Table 2. Occurrence of Any Atopic Disease During the First 2½ Years of Age in 669 Children in Relation to Vaccination and Parental History of Bronchial Asthma, Atopic Dermatitis, or Allergic Rhinitis*

		Vaccine Group Assignment, % of Children		
Parental History	No. of Subjects	2-c or 5-c	WC	DT
None	279	25.0	21.1	22.0
Mother	241	37.5	32.1	34.6
Father	227	38.4	35.7	33.3

**No significant differences were found between the vaccine groups. Abbreviations are explained in the footnote to Table 1.*

more frequent in children vaccinated with the 2-c vaccine than in the WC-vaccinated children (P = .08).

The prevalence of environmental tobacco smoke, dampness in the home, indoor pets, preterm birth, and gender did not differ significantly between the 4 groups (**Table 1**). There were, however, fewer children with a family history of allergic disease in the DT-vaccinated children than in the 2 acellular vaccine groups (90/172 vs 220/360; P = .05). When stratifying for family history of allergic disease, no significant differences in atopic manifestations were found between the children in the different vaccine groups (**Table 2**).

Risk estimates for atopic disease during the first 2½ years of life were obtained using a logistic regression model (**Table 3**). The risk in the DT group was estimated to be 22.5% in children with no parental history of allergic disease. The risk was estimated to decrease by 1.7 percentage points for the WC vaccine (upper 95% confidence limit, 6.2 percentage points). The figures correspond to an 8% reduction and 28% increase, respectively. The corresponding figures for children immunized with a component vaccine was an increase by 2.3 percentage points (single-sided upper 95% confidence limit, 9.3), corresponding to a 10% and 41% increase, respectively. The percentages all refer to children with no parental history of allergic disease. The pattern was similar in children with single and double heredity.

The prevalence of adverse effects was similar in atopic and nonatopic children, with the exception that a nodule

Table 3. Estimated Risk (From a Regression Model) for Atopic Disease During the First 2½ Years of Age*

Parental History of Allergic Disease	Estimated Risk in Control Group	Estimated Increase in Risk in Treatment Groups		Upper 95% Confidence Limits of Increase	
		WC	2-c and 5-c	WC	2-c and 5-c
None	17.5	2.3	0.3	6.2	4.1
1 Parent	23.1	2.9	0.4	7.5	5.4
Both parents	41.4	2.3	0.2	8.1	5.9

*Abbreviations are explained in the footnote to Table 1. Estimated risks in the control group are expressed as percentage values. Estimated changes in risk are expressed as a reduction or increase in these percentage points. For example, a risk increase of 2.3 corresponds to a 10% increase over the control group in the children receiving component vaccine.

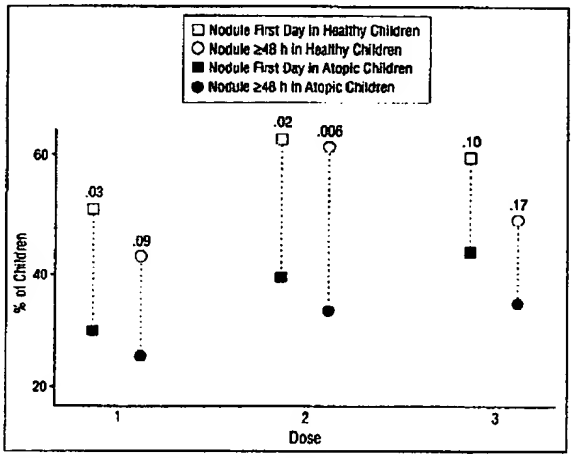

Figure 3. *Prevalence of a nodule at injection site after each of 3 injections with whole-cell pertussis vaccine (at 2, 4, and 6 months of age) in 137 children, stratified according to the presence or absence of atopic disease during the first 2½ years of life. Values at the top of symbols indicate levels of significance for differences between children with and without atopic disease. No significant differences were found between atopic and nonatopic children in any of the other groups.*

at the injection site after WC vaccination was more often reported in the nonatopic children (**Figure 3**). The most common adverse effects of the vaccines were redness (mean for all vaccine groups, 14%, 31%, and 39% after the first, second, and third injections, respectively), swelling (19%, 42%, and 48%), and fever (22%, 30%, and 33%). The incidence of adverse effects increased significantly with each dose given (for swelling and redness, $P<.001$) in children vaccinated with acellular pertussis vaccines or DT vaccine. The WC vaccine was associated with a similar high incidence of adverse effects after all 3 injections.

Forty-seven children had verified pertussis during the study period, 25 children in the DT group, 13 in the 2-c group, 8 in the WC group, and 1 in the 5-c group ($P<.001$). Pertussis was associated with an increased cumulative incidence of bronchial asthma, ie, 19% vs 9% in uninfected children ($P=.03$). Other atopic diseases also tended to be more frequent, although not significantly, among the children with confirmed whooping cough (40% vs 29%; $P=.10$).

COMMENT

The incidence of sensitization and manifestations of atopic diseases during the first 2½ years of life was largely similar after vaccination with any of 3 pertussis vaccines and placebo. There were several reasons to suspect that pertussis immunization could be associated with an increased risk for atopic manifestations. First, pertussis toxin is a potent adjuvant for IgE induction in animals,[7] and second, a strong IgE response can be obtained to pertussis toxin from purified vaccines.[8] Furthermore, primed T cells from children immunized with acellular vaccines secrete high levels of interleukin 5 and relatively low levels of interleukin 2 and interferon γ following specific antigen stimulation in vitro, ie, a mixed T_H1/T_H2 cytokine profile.[19]

Experiments in mice have shown that injection of *B pertussis* induces susceptibility to various chemicals,[20-22] and cold air,[23] indicating a functional β-receptor blockade. The immunological effects could possibly be explained by increased intracellular levels of cyclic adenosine monophosphate in lymphocytes induced by *B pertussis*[24] and thereby a shift toward a T_H2-like response.[25]

On the other hand, peripheral blood T cells from children with whooping cough secrete interferon γ but not interleukin 5 on antigen stimulation, implying that immunity generated by natural infection is mediated by T_H1-like cells.[26] Analysis of blood samples from children after immunization with WC pertussis vaccines revealed a similar cytokine profile.[19]

It is well known that families with allergic diseases tend to be overrepresented in allergy studies. There was, however, no significant difference regarding symptoms associated with allergy between participants in the present study related to allergy and the children who only participated in the efficacy part of the pertussis trial.[13]

We intended to study whether pertussis vaccination of infants would increase the risk of atopic disease and were fortunate to obtain data in a randomized and controlled experiment. Even though 669 children completed the trial, the estimated risk levels had large margins of error. Aiming at an 80% power to detect a 10% increase in risk rate, a treatment group and a control group with nearly 4000 infants in each would have been needed. As each group in our study consisted of about 175 infants, any true differences would have to be nearly 50% to obtain an 80% power of detecting the differences. This is acceptable as the main purpose of the investigation was to detect a largely increased risk similar to that reported by Odent et al[11] for a WC vaccine. A similar vaccine was included in the present study.

The study reported by Odent et al[11] was retrospective and not randomized. Considering the relatively small

size of the study groups and that there were only 30 cases of asthma, it is not surprising that they were not able to conduct a comprehensive analysis of possible bias. In contrast, our study was prospective and the problems of bias were addressed through randomization. The results indicate that it is unlikely that WC pertussis vaccination increases the risk of atopic disease to up to 2½ years by more than 4% (single-sided upper 70% confidence limit). It may be argued that the observation period was too short to detect allergic respiratory disease. There is reason to believe, however, that a majority of the children who will develop asthma or rhinitis during the next few years were already identified as atopic during the observation period since they were often already sensitized and/or have had atopic dermatitis during infancy.[27] It seems presently reasonable to conclude that WC pertussis vaccination is not associated with a major increase in the risk of atopic disease.

Because observed results were similar for the 2 acellular vaccines, the groups were merged in the final analysis. The estimated risks of atopy following acellular pertussis vaccination were about 10% larger than the estimated control group risk levels. Our results indicate a possible small increase in the risk of atopic disease after acellular pertussis vaccines. The upper 95% confidence limit for an increased risk was considerable, however. In the large Swedish pertussis vaccine trial,[14] the parents answered questions concerning symptoms of itching and wheezing in 9617 children. Similar frequencies of the symptoms were reported from all the 4 vaccine groups. With the acellular vaccines, the upper 95% confidence limit was 5.7% above the level in the control group for wheezing and 13.5% for itching. These results suggest that any negative effects of acellular vaccines are not much larger than 10%. Whooping cough is a debilitating disease and, in infancy, there may be serious complications. The reasonable conclusion seems to be that acellular vaccines would at most be associated with a small to moderate increase in atopy.

We also observed an association between pertussis and asthma. This could, for instance, be due to a causal relationship in that pertussis might increase the risk of later becoming asthmatic, eg, by inducing β-receptor blockade.[28] It might also be due to transient bronchial hyperreactivity after whooping cough.[29]

At present, we recommend pertussis vaccination during early infancy, independent of any family history of atopic disease.

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Reprints: Lennart Nilsson, MD, Department of Health and Environment/Pediatrics, University Hospital, 581 85 Linköping, Sweden.

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BRIEF REPORTS

Is Infant Immunization a Risk Factor for Childhood Asthma or Allergy?

Trudi Kemp,[1] Neil Pearce,[1] Penny Fitzharris,[1] Julian Crane,[1] David Fergusson,[2] Ian St. George,[3] Kristin Wickens,[1] and Richard Beasley[1]

The Christchurch Health and Development Study comprises 1,265 children born in 1977. The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years; in the immunized children, 23.1% had asthma episodes, 22.5% asthma consultations, and 30.0% consultations for other allergic illness. Similar differences were observed at ages 5 and 16 years. These findings do not appear to be due to differential use of health services (although this possibility cannot be excluded) or confounding by ethnicity, socioeconomic status, parental atopy, or parental smoking. (Epidemiology 1997;8:678–680)

Keywords: asthma, allergy, immunizations, children.

The prevalence of asthma and allergic disease has increased in many countries,[1–4] and there has been a great deal of speculation as to possible causes,[5–11] including the possible role of immunization in promoting allergic sensitization.[12] For example, pertussis vaccination acts as an adjuvant for antigen-specific responses in laboratory animals[13–15]; a specific immunoglobulin E (IgE) response to pertussis toxin itself has been identified in children receiving pertussis immunization[16]; and vaccination with some other organisms enhances histamine release in laboratory animals.[17,18] In addition, two studies have found that pertussis infection increased the risk of atopy,[19,20] and another study found that aluminum-adsorbed vaccines produce greater IgE responses.[21] It is therefore theoretically possible that immunization may contribute to the development of allergic disease, whether through reducing clinical infections in infancy,[12] or through the direct IgE-inducing effects of the vaccines themselves and/or the potentiating adjuvants. We have therefore examined data from a New Zealand cohort study to investigate the relation between infant immunization and subsequent allergic disease.

Methods

The Christchurch Child Development Unit comprises 1,265 children born in 1977.[22] Information on immunizations, asthma, and other allergic disease (collected annually until age 16 years) was obtained from (1) a medical diary supplied to all mothers, (2) direct questioning of the mother about medical contacts, and (3) cross-checking with the family doctor when maternal reports or diary records were vague or inconsistent. Infants were scheduled to receive diphtheria/pertussis/tetanus (DPT) and polio immunizations at ages 3 and 5 months and measles immunization at 12–15 months; we did not consider subsequent immunizations, since our hypothesis focused on infant immunizations. Data on asthma, eczema, and other allergies (including rhinitis, food allergy, and urticaria, but excluding drug allergies) were categorized as to whether children had consultations (reported medical contacts) or episodes (consultations plus reported episodes not medically seen) up to ages 5, 10, and 16 years. A child was assigned to a negative category only if there were complete negative data for that child; a positive category was allocated if any episodes or consultations took place, whether or not the data were complete.

We analyzed the data using the Mantel-Haenszel summary risk ratio[23,24] and Fisher exact methods where appropriate.

From the [1]Wellington Asthma Research Group, Department of Medicine, and [2]Department of the Dean, Wellington School of Medicine, Wellington, New Zealand; and [3]Christchurch Health and Development Study, Christchurch School of Medicine, Christchurch, New Zealand.

Address correspondence to: Neil Pearce, Wellington Asthma Research Group, Wellington School of Medicine, P.O. Box 7343, Wellington South, New Zealand.

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TABLE 1. Characteristics of the Immunized and Nonimmunized Groups

	Immunized (N = 1,184)		Nonimmunized (N = 23)		Total (N = 1,207*)	
	Number	%	Number	%	Number	%
Gender						
Female	587	49.6	12	52.2	599	49.6
Male	597	50.4	11	47.8	608	50.4
Ethnicity						
Polynesian	164	13.9	9	39.1	173	14.3
European/other	1,020	86.1	14	60.1	1,034	85.7
Socioeconomic status†						
Classes 1 and 2	248	20.9	3	13.0	251	20.8
Classes 3 and 4	634	53.6	6	26.1	640	53.0
Classes 5 and 6	302	25.5	14	60.9	316	26.2
Parental history of						
Asthma	214	18.1	5	21.7	219	18.1
Eczema	253	21.4	6	26.1	259	21.5
Allergic rhinitis	356	30.1	5	21.7	361	29.9
Parental smoking 0–5	650	56.2	19	82.6	669	56.7
Pet ownership 0–5	923	79.8	21	91.3	944	80.4

* Totals do not sum to 1,207 where data are not complete.
† Elley-Irving socioeconomic index for New Zealand occupations.

Results

Only 23 (1.8%) children in the cohort were recorded as having received neither of the two scheduled DPT and polio vaccinations due at 3 and 5 months. They were more likely to be in a low socioeconomic group, Polynesian, or exposed to parental smoking, but there was little difference with respect to gender, pet ownership, or parental histories of asthma, eczema, or allergic rhinitis (Table 1).

Table 2 shows the risk ratios (RRs) (with Fisher exact confidence intervals) for various outcomes. The 23 nonimmunized children had no episode or consultation for asthma or consultation for other allergies before age 10 years; between ages 11 and 16 years, some events were recorded, but the risks were still relatively low. There was little association between immunization and eczema (Table 2), or for consultations for gastrointestinal symptoms before age 2 years [RR = 1.3; 95% confidence interval (CI) = 0.6–3.3], reported gastrointestinal symptoms before age 2 years (RR = 1.0; 95% CI = 0.6–1.8), or reported measles, rubella, chicken pox, or mumps (not shown in table).

We were not able to adjust for all potential confounders simultaneously because of the small numbers involved, with some analyses involving no cases in the nonimmunized group. Nevertheless, we did attempt to assess confounding by: (1) assessing whether potential confounders were related to the outcome in the overall dataset, and (2) for the outcomes with some cases in the nonimmunized group, adjusting for each confounder in turn. Ethnicity, low socioeconomic status, parental smoking, and pet ownership (Table 1) had no association, or a positive association, with the outcome measures [for example, at age 10 years, Polynesian ethnicity was not associated with asthma episodes (RR = 1.0), asthma consultations (RR = 1.0), or allergy consultations (RR = 1.0); the corresponding relative risks were 1.3, 1.4, and 0.9 for socioeconomic groups 5 and 6; 1.1, 1.1, and 1.0 for parental smoking; and 0.8, 0.9, and 1.0 for pet ownership]. There was also little evidence of confounding in the adjusted analyses. For example, to age 16 years, the relative risk for asthma episodes was 2.9 (Table 2); this value became 2.8 when adjusted for ethnicity, 3.0 when adjusted for socioeconomic status, 3.0 when adjusted for parental smoking, and 2.8 when adjusted for pet ownership. The corresponding figures were 2.7, 2.7, 2.9, 2.8, and 2.6 for asthma consultations; and 5.6, 5.7, 5.7, 5.7, and 5.6 for allergy consultations. Thus, there is little evidence that the findings in Table 2 are due to confounding by the factors shown in Table 1.

We also examined associations between infant measles, mumps, rubella, or chicken pox infections, or measles vaccination, and the outcome measures described above, but we found no strong association. For example, for asthma episodes up to the age of 10 years, the relative risk was 1.2 (95% CI = 1.0–1.4) for reported measles infection and 1.0 (95% CI = 0.9–1.1) for measles vaccination.

TABLE 2. Asthma and Allergies in the Immunized and Nonimmunized Groups*

	Immunized		Nonimmunized			
	Yes	No	Yes	No	Risk Ratio	95% CI
Ages 0–5 years						
Asthma episodes	133	936	0	20	∞	0.7–∞
Asthma consults	134	935	0	20	∞	0.7–∞
Allergy consults	165	899	0	16	∞	0.7–∞
Eczema consults	283	798	4	16	1.3	0.5–4.9
Ages 0–10 years						
Asthma episodes	234	777	0	17	∞	1.05–∞
Asthma consults	227	782	0	17	∞	1.03–∞
Allergy consults	302	704	0	13	∞	1.05–∞
Eczema consults	334	686	5	13	1.2	0.5–3.7
Ages 0–16 years						
Asthma episodes	315	625	2	15	2.9	0.8–23.6
Asthma consults	297	641	2	15	2.7	0.7–22.3
Allergy consults	404	530	1	12	5.6	1.0–222.6
Eczema consults	398	552	7	12	1.3	0.5–2.8

* Totals do not sum to 1,207 where data are not complete.

Discussion

The findings presented here are consistent with the hypothesis that some component of infant immunization may increase the risk of developing asthma in childhood. An important limitation of our data is the small nonvaccinated group. The vaccinated differed from the nonvaccinated with respect to several factors, including parental smoking,[25] Polynesian ethnicity,[26] and lower socioeconomic status,[27] but these factors have been found in previous New Zealand studies, and in the current study, either to be positively related or to have no association with asthma symptoms or diagnosed asthma.

All the outcome variables used in this analysis have a health service component, and it is possible that health service access or utilization, or recognition of symptoms, was different for the nonvaccinated children. There was little difference, however, between the vaccinated and nonvaccinated groups with respect to consultations for eczema or gastrointestinal symptoms, or for reported measles, rubella, chicken pox, or mumps. Nevertheless, we cannot exclude the possibility that the findings are due to differences in health service access or use.

Three previous studies have examined immunization, and the findings are inconsistent. Butler and Golding[28] found no association between pertussis immunization and wheeze at age 5 years, but a lower risk of eczema. Odent *et al*[29] found that pertussis vaccination increased the risk of diagnosed asthma. Nilsson and Storsaeter[30] conducted a randomized trial of two types of acellular pertussis vaccine, whole cell pertussis vaccine and no pertussis vaccine; they found no differences in a telephone survey of wheeze, itching, and sneezing at age 2 years. These findings are, to some extent, reassuring with regard to pertussis immunization, but not necessarily about all immunizations, since all children in our study also received diphtheria and tetanus immunizations. We have also had the opportunity to reanalyze the Dunedin Multidisciplinary Health and Development Study,[31] involving 1,037 children born in 1972–1973, but only five children were recorded as having no vaccination before the age of 3 years.

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